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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,899	06/04/2001	Nnochiri N. Ekwuribe	9233-54	5139

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,899	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-11,16-30,40,41,46-48,50,52 and 68-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16,18-23,25-28,68-71,79,81-86,88-92 and 97-100* is/are allowed.

6)☒ Claim(s) *1-3,7-11,17,29,30,40,41,46-48,50,52,72-78,80,93-96,101 and 102* is/are rejected.

7)☒ Claim(s) *24 and 87* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant is advised that should claims 95 and 96 be found allowable, claims 40 and 41 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 40 and 95 are identical in scope, and claims 41 and 96 are identical in scope.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52, 72-78, 80, 93-96, 101 and 102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-142 of copending Application No. 10/235,381. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '381 application anticipate the instant claims. Note that the '381 application claims monodispersed mixtures of an insulin drug-oligomer conjugate (see, e.g., claims 21, 45, and 67) where the oligomer can be $C(=O)\text{-}(CH_2)_5\text{-}(OC_2H_4)_7\text{-}OCH_3$ attached to LysB29 (see, e.g., claims 18, 24, 42, 48, 64, 70, and 71).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52, 72-78, 80, 93-96, 101 and 102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-230 of copending Application No. 10/075,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '097 application anticipate the instant claims. Note that the '097 application claims monodispersed mixtures of an insulin drug-oligomer conjugate where the oligomer is $C(=O)-(CH_2)_5-(OC_2H_4)_7-OCH_3$ attached to LysB29 (see, e.g., claims 170, 183, and 186).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52, 72-78, 80, 93-96, 101 and 102 are directed to an invention not patentably distinct from claims 1-230 of commonly assigned 10/075,097. Specifically, see the above provisional obviousness-type double patenting rejection.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned application serial no. 10/075,097, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was

made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

6. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52, 72-78, 80, 93-96, 101 and 102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 10/461,199. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '199 application anticipate the instant claims. Note that the '381 application claims substantially monodispersed mixtures of an insulin drug-oligomer conjugate where the oligomer can be $C(=O)-(CH_2)_5-(OC_2H_4)_7-OCH_3$ (see claims 11 and 22) where the oligomer can be attached to LysB29 (see claims 6 and 17).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52, 72-78, 80, 93-96, 101 and 102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-79 of copending Application No. 10/382,155. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '155 application anticipate the instant claims. Note that the '155 application claims monodispersed mixtures of an insulin drug-oligomer conjugate (see, e.g., claims 16 and 50)

where the oligomer can be $C(=O)-(CH_2)_5-(OC_2H_4)_7-OCH_3$ attached to LysB29 (see, e.g., claims 13, 23, 47, and 57).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52, 72-78, 80, 93-96, 101, and 102 are rejected under 35 U.S.C. 103(a) as being obvious over the Radha Krishnan et al abstract (1999 Nat. Meet. Amer. Assoc. Pharm. Scient.; Reference 65 of the Information Disclosure Statement filed November 24, 2003) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. The Radha Krishnan et al abstract teaches methoxy-polyethylene glycol having n subunits conjugated through hexanoic acid to the amino group of the LysB29 residue of human insulin. The conjugates are orally active, are enzymatically stable, and have improved amphiphilic characteristics and lower aggregation. The Radha Krishnan et al abstract does not teach PEG having seven subunits (i.e., n=7), and does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines

3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal PEG sizes for the PEG component taught by the Radha Krishnan et al abstract because polymer size is an art-recognized result-effective variable which is routinely determined and optimized in the polymer arts, and because Delgado et al teach the desirability of optimizing PEG length in order to isolate the specific conjugate possessing optimal biological properties. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to prepare the PEG-Hex-insulin conjugates of the Radha Krishnan et al abstract using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by the Radha Krishnan et al abstract; because the use of discrete length PEG in the conjugates of the Radha Krishnan et al abstract would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

10. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52, 72-78, 80, 93-96, 101, and 102 are rejected under 35 U.S.C. 103(a) as being obvious over the Radha Krishnan et al abstract (1999 Nat. Meet. Amer. Assoc. Pharm. Scient.; Reference 65 of the Information Disclosure Statement filed November 24, 2003) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO

Patent Application 97/14740 as applied against claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52, 72-78, 80, 93-96, 101, and 102 above, and further in view of the Harris et al article (J. Macromol. Sci., Vol. C25, pages 325-373). As noted above, while the Radha Krishnan et al abstract does not teach the polymer size for insulin conjugates in particular, the Harris et al article teaches that when using PEG-protein conjugates, PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to optimize result-effective conjugate properties, e.g., polymer size, as taught by the Harris et al article for the PEG-insulin conjugates of the Radha Krishnan et al abstract in order to maximize the conjugates' desirable properties.

11. Applicant's arguments filed September 8, 2003 have been fully considered but they are not persuasive.

Because this application is not otherwise in condition for allowance, the provisional obviousness-type double patenting rejections set forth above can not be withdrawn in accordance with the procedures of MPEP 822.01.

The rejection under 35 U.S.C. 103(a) based upon the Radha Krishnan et al article (Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., Vol. 27, pages 1038-1039) as the primary reference is withdrawn. The declaration filed September 8, 2003 shows that the Radha Krishnan et al article is not by another and therefore is not available as prior art under 35 U.S.C. 102(a).

The rejection under 35 U.S.C. 102(e) based upon Ekwuribe et al (U.S. Pub. No. 2003/0050228) is withdrawn in view of the declarations filed September 8, 2003 and November

24, 2003, which show that the disclosure of the reference relied upon in the rejection was not by another and therefore is not available as prior art under 35 U.S.C. 102(e).

The Radhakrishnan et al abstract (Proceed. Intl. Symp. Control. Rel. Bioact. Mater., Vol. 25, pages 124-125; Reference 64 of the Information Disclosure Statement filed November 24, 2003) has been carefully considered but is not deemed to teach or suggest the instant claimed invention. The Radhakrishnan et al abstract teaches mixtures of modified insulins, and does not provide any motivation or suggestion to isolate or purify any single one of these modified insulins.

The Uchio et al article (Advanced Drug Delivery Reviews, Vol. 35, pages 289-306; Reference 84 of the Information Disclosure Statement filed November 24, 2003) has been carefully considered but is not deemed to teach or suggest the instant claimed invention. The Uchio et al article is limited to the use of succinic acid rather than hexanoic acid to link PEG to its insulin, and teaches away from linking PEG to insulin sites other than at PheB1.

12. Claims 16, 18-23, 25-28, 68-71, 79, 81-86, 88-92, and 97-100 are allowed. Claims 24 and 87 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

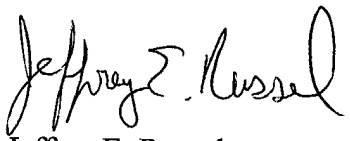
13. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on November 24, 2003 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

PLEASE NOTE: Sometime on or around January 6, 2004, the examiner will be moving to the new USPTO headquarters. At that time, the examiner's phone number will change to (571) 272-0969. After January 6, it is recommended that Applicants attempt to contact the examiner at the new phone number if they are unable to reach him using the old number.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Technology Center 1600 for formal communications is (703) 872-9306; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1600 receptionist is (703) 308-0196.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
December 29, 2003